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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,223	02/22/2002	Vladimir P. Torchilin	06558-004006	2707

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,223	TORCHILIN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *December 20, 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *8-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/22/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed December 20, 2004 in response to the Office Action of August 24, 2004 is acknowledged and has been entered. However, upon review and reconsideration the restriction requirement mailed August 24, 2004 is hereby vacated. The Declaration filed March 30, 2005 is acknowledged and has been entered. Claims 8-12 are currently under prosecution.

2. Applicant's notation of Examiner's statement that, upon allowance of claim 8, the restriction requirement as to the linked inventions will be withdrawn is acknowledged. Applicant's election, without traverse, of Group I, Claims 8-9, 11-12 is acknowledged. However, given the statement above, Applicant's election is rendered moot.

Specification

3. The specification on page 1 should be amended to reflect the status of the parent applications.

Claim Rejections - 35 USC 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

5. Claims 8-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

It is noted that the claims as currently constituted do not limit the claimed invention to mammals that do not have a tumor burden, but rather limit the

invention to mammals at risk of malignant cell growth. Given this wording, it is reasonable to assume for examination purposes that both mammals that have no tumor burden and those that do have a tumor burden can be at risk of malignant cell growth. That is those mammals without any tumor burden are at risk of de novo malignant cell growth while those with tumor burden are at risk of additional malignant cell growth.

The claims are drawn to a method of inhibiting malignant cell growth in a mammal at risk for malignant cell growth comprising administering an amount of nucleosomes effective to elicit the production of sufficient antinuclear autoantibodies (ANA) to inhibit malignant cell growth in the mammal, wherein the nucleosomes comprise mammalian DNA/bacterial DNA are liposome encapsulated, wherein the mammal is a human. This includes (A) a method of inhibiting malignant cell growth at any time prior to onset of malignant cell growth as well as (B) a method of inhibiting malignant cell growth in a an individual that has malignant cell tumor burden.

The specification teaches that individuals considered at risk for developing cancer may benefit particularly from the invention, primarily because prophylactic treatment can be begun before there is any evidence of a tumor. Individuals at risk include those with a genetic predisposition and those who have been inadvertently exposed to nuclear radiation or a carcinogenic substance (p. 3, lines 16-23). The specification further teaches that the nucleosomes can be administered before the appearance of a tumor (p. 2, lines 24-29). The enablement of the claimed method appears to be based on the exemplification of a mouse model wherein the mice are first vaccinated with a nucleohistone preparation and then 9 days later are inoculated with either lymphoma or Lewis carcinoma cells. It was found that tumor

production in nucleosome vaccinated mice was inhibited when compared with sham vaccinated mice (lines 14-19).

One cannot extrapolate the teaching of the specification to the enablement of the claims because:

(A) the claims are drawn to the inhibition, which reads on prevention, of malignant cell growth in mammals at risk of developing said growth. Although the specification defines individuals at risk, as disclosed above, there is no teaching in the specification as to when the method is to be initiated other than that the prophylactic treatment can be begun before there is any evidence of a tumor. Certainly the majority of the population of the United States has been inadvertently exposed to carcinogenic substances through exposure, for example, to second hand smoke and all of the population has been exposed to nuclear radiation from the sun. Clearly not all of these individuals or even the majority of these individuals develops a malignancy associated with the exposure and it is not clear how the claimed method would be used for these individuals. Further, although individuals have been identified who have genetic predisposition for developing cancer, it is well known in the art that not all of these individuals eventually develop the disease and that the identification of individuals with genetic risk is a developing, but not yet developed art. The undeveloped nature of this art is exemplified by Cotterchio et al, 2000, Chronic Diseases in Canada, (Electronic Version downloaded from http://www.phac-aspc.gc.ca/publicat/cdic-mcc/21-2/f_e.html) who reveal that the reference is the first population-based family colorectal cancer registry developed within Canada and since this is a novel undertaking, there are no published reports with which to compare the data (see discussion, para 1). The reference specifically states that a high response rate is important in order to ensure

that the families in the registry are representative of the population from which they are selected. However, obtaining high response rates in genetic family studies of colorectal cancer is especially challenging because of the time commitment required to complete the many phases of the data collection, issues of confidentiality and the high mortality rate among the cancer cases (see discussion, para 1). The reference specifically teaches that future research is needed to identify methods of overcoming these barriers to participation. Further the reference teaches that response bias arising from differences in characteristics between participants and non-participants is always a concern in epidemiologic studies when response rates are low, as it may lead to biased estimates of prevalence and association. Finally, the reference concludes that the study offers exciting opportunities for the study of genetic and environmental factors associated with colorectal cancer as well as providing a source for the development of chemoprevention trials, cohort studies and gene discovery projects. The reference clearly teaches that there are challenges and problems associated with the development of familial colon cancer registries which may lead to biased estimates. The reference neither teaches nor suggests how to identify which patients are at risk and should be candidates for any particular method of inhibiting malignant cell growth or when to begin these protocols. Based on the information in this reference, it is clear that the assessment of patient risk based on familial history is a developing but not a well-established art. The reference clearly suggests the lack of predictability of the art when concluding that the familial history study is useful for the ***development*** (emphasis added) of chemoprevention trials.

Further, Apantaku, Breast cancer diagnosis and screening, American Family Physician (2000). (Electronic version, downloaded from http://www.healthlibrary.com/doctors2/breastcancer2.html) reveals that most women with breast cancer have no identifiable risk factors (p. 596, col 2). The reference further teaches that women who have pre-menopausal first-degree relatives with breast cancer have a three- to fourfold increased risk of developing breast cancer than women who do not. The risk factor of their having second-degree relatives with breast cancer has not been quantified (p. 596, col 2). The reference further teaches that genetic testing is controversial and raises issues about the reliability of tests and the use made of test results (p. 597, col 1). A woman who tests negative for a particular mutation may still be at risk for developing breast cancer from a sporadic mutation or a preexisting unidentified mutation. False negative results are also possible. (P. 597, col 1). The reference then goes on to detail factors that may be involved with increased risk of breast cancer (page 597-598) and suggests change of diet may alter personal risk factors (p. 598, col 1). However, it must be emphasized that the language used in the reference is "may be involved", "may alter personal risk factors". The teachings here are clearly speculative at best. Finally, although one group is identified as being at increased risk, there is no teaching of how or when to begin an intervention protocol.

A review of Martin et al (Journal of the National Cancer Institute, 92:1126-1135) reveals that it is hoped that identification of genetic and environmental factors that contribute to the development of breast cancer will enhance prevention effects. The reference reviews the state of the art of breast cancer genetic components of susceptibility to breast cancer from the standpoint of both human genetics and rat models (see abstract) . The reference specifically states that despite

numerous studies published to date, the role of modifier genes in breast cancer susceptibility remains to be elucidated. The resolution of ambiguous results will require further carefully designed studies with sufficient sample sizes to detect small effects. The reference concludes that great strides have been made in determining the disease etiology but that further investigation is necessary and that these studies will be crucial to evaluate the importance of new genes involved in breast cancer etiology so that scientists can define better therapies and cancer prevention (p. 1132, col 1) Finally, there is no teaching of how or when to begin an intervention protocol. It is clear from the teachings of this reference that the art of identifying an individual at risk for malignant growth is a developing but as yet undeveloped art. The reference provides no guidance on how to determine which patients are at risk or when to administer treatment in order to inhibit the malignant cell growth for which the individual is at risk.

These references clearly point to the undeveloped nature of the art of reading cancer markers for the assessment of the probability of developing cancer and do not teach what interventions would have a reasonable expectation of success nor teach when or how those protocols should be administered. Further, it is noted that each of these references was published in 2000. The art recognized undeveloped nature of the art makes it clear that one of the art would not have expected to successfully use the claimed methods at the time the invention was made in 1996.

The specification does not provide either guidance on or exemplification of how to determine which of these individuals at risk would be candidates for the method. Although the inhibition of tumor formation is exemplified in the specification, as disclosed above, the model used cannot be correlated to inhibition of malignant growth in humans as broadly claimed because it would not be

expected that malignant cell growth would be initiated by the injection of viable tumor cells into an individual. Thus, it is clear that the data presented is not commensurate in scope with the claims as written.

Taken together, the evaluable references submitted clearly demonstrate the undeveloped nature of the cancer risk assessment art. The methods of "use" in the specification are general teachings drawn to administration of the nucleosome vaccine. There is no teaching of parameters to determine which mammals to inject or when or how to determine what protocols would enable the invention to function as claimed. In view of the teachings of the specification and the art of record, it is not possible to predict when or how to use the broadly claimed method with a reasonable expectation of success.

(B) The specification teaches as set forth above and further teaches/hypothesizes, based on the 2C5 data, that the induction of such antibodies *in vivo* provides a means for treating neoplastic cell growth (p. 2 lines 5-17) and states that accordingly the invention features a method of treating neoplastic cell growth in an animal (p. 2). The specification further teaches that the invention is based on the discovery that antibody 2C5 has been shown to dramatically inhibit the development of an aggressive cancer *in vivo* (p. 5, lines 27-30) to bind to the surface of tumor cell lines but not to the surface of normal, non-malignant cells (p. 6, lines 1-5) and that two additional ANAs obtained from aged, healthy Balb/c mice have also been shown to bind to the surface of human and rodent tumor cell lines but not to normal cells (p. 6, lines 10-14). The specification further exemplifies the restricted binding of antibody 2C5 to nucleosomes (see Table 1, page 8) and exemplifies nucleosome immunization of non-autoimmune adult mice prior to inoculation with tumor cells (see pages 21-22) which led to inhibition of

the development of tumors and suggests that immunization with nucleosomes should also be effective when a tumor is already present in the host and discloses a prophetic example for the analysis of this aspect of the invention (pages 22-24).

One cannot extrapolate the teaching of the specification to the enablement of the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed method would function as claimed based only upon the demonstration that antibody 2C5 inhibited the development of an aggressive cancer *in vivo*, that it binds to nucleosomes and tumor cell lines *in vitro* (and that two other ANA's also bind to tumor cell lines *in vitro*) and that nucleosome immunization prior to inoculation with tumor cells inhibited the development of the tumors. Although it appears that nucleosome immunization in this particular model inhibits the attachment of tumor cells injected 9 days after the immunization procedure, this model is not commensurate in scope with the claimed invention and cannot be correlated to or extrapolated to the treatment of a mammal who already has a tumor burden. This is especially true in view of the teaching of Boon (Adv Can Res, 1992, 58:177-210) who teaches that for active immunization in human

patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). Thus it could not be predicted, given the information in the specification and in the art, that the invention would function as claimed in a mammal that has a tumor burden. Further, Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by therapeutic agents, in the instant case ANA (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by therapeutic agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat treatment strategies and if this is true, designing effective therapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed method will function as claimed based on the evidence provided in the specification. Further, it was well known in the art at the time the invention was made that a substantial human population expresses antinuclear autoantibodies and that at least a subset of the

population are patients with a tumor burden. It is not clear how the addition of nucleosomes to increase the population of ANAs would effectively treat a tumor which is not treated by the autoantibody population already in place since it is clear that it would be expected, given the teaching of Boon, that the mammal would be tolerized to the antigen. Further, as drawn to the cell line studies, it is well known that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. For example, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a

lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, an anti-tumor agent, in this case the produced ANAs must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have a alternate means of survival despite action at the proper site for the drug. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the anti-tumor agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood, that affect both the administered nucleosomes and any ANAs produced, are important parameters in achieving successful therapy. The agents may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the agents and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the agents may not otherwise reach the target because of the inability to penetrate tissues or cells where activity is to be exerted, may be absorbed by fluids, cells and tissues where the agent has no effect, circulation into the target area may be insufficient to carry the agent and a large enough local concentration may not be established. Finally, the specification provides neither guidance on nor exemplification of dosages or routes of administration required so that the invention would function as claimed. There is

no teaching of how often to administer the nucleosomes to produce sufficient autoantibodies to function as claimed, at what stage of symptom on-set to administer the nucleosomes, what mode of administration will be effective and how long to continue administration. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed methods will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

6. The arguments set forth in the paper filed October 7, 2002 and the Declaration submitted March 30, 2005 are relevant to the instant rejection.

Applicant argues that the Torchilin Declaration shows that one can inhibit malignant cell growth in a mammal at risk for such growth by administering nucleosomes to the mammal. Further, the data shows that one can inhibit malignant cell growth even if ANAs are already present in the mammals when the nucleosomes are administered wherein it is demonstrated that administration of nucleosomes increased the titre of ANAs in nucleosome-treated animals when compared with controls. The titre increased five-fold over time. Further, the average volume and average weight of the tumors in the nucleosome-treated animals was consistently less than the average volume and average weight of the tumors in the control animals.

The arguments and the Declaration were carefully considered by Examiner but not found to be persuasive because, as set forth above, Examiner has reasonably interpreted the claims to encompass prevention of cancer and inhibition

of cancer cell growth in a mammal with tumor load. The instant animal model, like that previously disclosed is not commensurate in scope with the claimed invention. Mammals at risk for malignant cell growth do not develop malignant cell growth by having the cells injected into their flanks. What Applicant has demonstrated is that active immunization can inhibit malignant cell growth in an animal model that is first vaccinated with nucleosomes and then had cancer cell lines injected subcutaneously. It appears that the experiments presented were undertaken, in part, to answer Examiner's questions concerning why (when cancer patients already express ANAs) active immunization with nucleosomes would be expected to inhibit malignant cell growth/prevent malignant cell growth in these patients at risk for malignant cell growth. However, once again the model is not commensurate in scope with the claimed invention. Clearly, a review of Figures 2 and 3 of the Declaration disclose that tumor growth was not prevented. Further, as referred to above, Fernandez-Madrid et al, of record clearly disclose that lung cancer patients present with significantly higher titres of ANAs than do normal controls and yet it does not appear that these ANAs are effective in inhibiting malignant cell growth of these stage III and stage IV tumors (see page 1384). Applicant's experiments do not address the question raised in view of Fernandez-Madrid et al because animal model was not drawn to mammals with a tumor load. Further, although it is clear that the ANA titre in the vaccinated animals is higher than that in the control animals, an examination of Figures 2-3 reveals that the effects of that vaccination on animals that are injected with tumor cells after boosting with nucleosomes is not significant as regards malignant cell growth. Although Dr. Torchilin states that the average volume and average weight of the tumors in the nucleosome-treated animals was consistently less than the average

volume and average weight of the tumors in the control animals, it is clear from Figures 2 and 3 that the results were so variable that significance was not established and although a trend appears to be in evidence, the meaning of this trend in terms of dosage and administration cannot be determined. Further, it is clear from the information in the Declaration that it is not possible for the claimed method to "prevent" the formation of tumor, even in the model instantly presented. Finally, the Declaration does not address issues raised previously and above drawn to identification of the candidate for active immunotherapy, when to start treatment and dosage to be used in patients who do not have cancer, that is for the prevention of cancer encompassed by the claims as currently constituted. The Declaration does not address issues drawn to patients with tumor load and tolerization. The Declaration and the arguments drawn thereto have been carefully considered but have not been found persuasive and the newly instituted rejection stands.

7. In the paper filed October 7, 2002, Applicant states that Examiners Ungar and Caputa advised Applicants to outline the arguments made previously and during the interview and that Applicants understood that these arguments would be sufficient to overcome the rejection. However, contrary to Applicant's understanding, although the Examiners did advise Applicant to outline the arguments it was made clear to Applicant that no decision would be made on the sufficiency of the arguments without a review of those arguments.

Applicant argues that although the process of deciding who is at risk for malignant cell growth is not an exact science, it is an endeavor routinely and necessarily undertaken by physicians in consult with one another and their patients. In support of this position, Applicants previously submitted a number of references and stated that if any individual was within those populations, they are candidates

for the method now claimed. Further, one of ordinary skill in the art would not have to resort to undue experimentation to determine whether a patient is "at risk" and thus this rejection should be withdrawn. The arguments and references have been previously considered and have not been found persuasive for the reasons of record. Contrary to Applicant's argument, the references previously submitted and carefully evaluated by Examiner conclusively showed that the art of risk assessment was a developing but as yet undeveloped art four years post filing. Given that information, it could not be predicted nor would it have been expected that one of ordinary skill could use the claimed invention with a reasonable expectation of success.

Applicant argues that because claim 8 now recites a method of inhibiting malignant cell growth in a mammal at risk for malignant cell growth the rejection of the claims drawn to a mammal that bears a tumor burden is now moot.

The argument has been considered but has not been found persuasive because the claims are broadly and reasonably interpreted to include mammals that bear a tumor burden because the claim is not limited to mammals that do not have a tumor burden, but is limited only to those at risk of malignant cell growth. It is clear that animals bearing a tumor burden are at risk of additional malignant cell growth. For this reasons, the rejection drawn to mammals with tumor burden has been reiterated.

Applicant argues that the presence of ANAs in certain populations in no way makes dosing unpredictable. In answer to Examiner's question as to why mammals in these populations develop malignancies, Applicant argues that if levels of ANAs in, for example elderly people, are not sufficient to prevent cancer, one would reasonably expect that higher levels must be generated in the method

now claimed. The argument has been considered but Applicant's unsubstantiated opinion is not found persuasive. Nothing in either the specification or the art of record provides information drawn to the dosage, method of administration, time of administration required in order to prevent cancer. Given the known presence of ANAs is some populations that develop cancers, it would appear that ANAs do not prevent cancer and it cannot be predicted or determined from the information in the specification whether or not vaccine that produces additional ANAs will function as claimed with a reasonable expectation of success.

Applicant points to Fernandez-Madrid et al (Clinical Cancer Res., 1999, 5:1393-1400, of record) that illustrates the type of information available about ANA levels in cancer patients. Fernandez-Madrid found that ANAs were more common in patients with biopsy-proven, locally advanced or metastatic lung cancer than in subjects without a history of cancer. Further, Fernandez-Madrid found that although autoantibodies are more prevalent in the elderly population, they are usually of low titer, unlike those reported here. The discussion of Fernandez-Madrid et al is acknowledged. However, Examiner is not clear as to what Applicant is asserting here since the rejection under discussion is drawn to prevention of cancer and not to cancer treatment. However, given the rejection set forth previously and above drawn to treatment of mammals with tumor burden with the claimed invention, given the titer of ANAs found in the cancer patients, it would not seem likely that administration of the claimed nucleosomes would be useful for treatment since the significantly higher than control titers found in the cancer patients disclosed did not successfully treat the patients.

Further, Applicant states that most significantly, Fernandez-Madrid finds some correlation between ANAs and PFS wherein it is stated that "some of these

antibodies were associated with prolonged survival without disease progression. Thus, there is at least some indication that naturally occurring levels of ANAs provide some protection against disease progression. This argument has been considered but has not been found persuasive since nowhere in the Fernandez-Madrid reference is there any suggestion that the ANAs are useful for inhibiting malignant cell growth.

Applicant argues that nothing that was known about ANAs or their level of expression in various populations would force one of ordinary skill in the art to resort to undue experimentation since empirical studies to determine effective doses are done routinely when bringing a therapeutic agent from laboratory studies to human clinical trials. The argument has been considered but has not been found persuasive because it cannot be predicted, based on the information in the specification and the art of record, whether or not the invention will function as claimed and given the unpredictability of the art, it cannot be determined with this information what, if any dose, would be effective.

Applicant argues that treatments with other antigens have been successfully extrapolated from murine models to clinical application and there is no reason to expect that one could not do the same here. Applicant further argues that human data is not required and that all FDA-approved agents have traveled a similar path from *in vitro* assay to animal models to clinical trials. The argument has been considered but has not been found persuasive because the art of inhibiting malignant cell growth with a nucleosome vaccine is an undeveloped art. For the reasons of record, the animal model used here is not commensurate in scope with the claimed invention and therefore cannot be extrapolated to a reasonable prediction of success. It is noted that MPEP 2164.03 teaches that "the amount of

guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In view of the complex nature of the claimed invention, the animal model used, the undeveloped nature of the art, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Applicant argues that there is contradictory evidence as to whether ANAs bind specifically only to nuclear material or whether they cross react with membrane proteins. Applicant submits an abstract and argues that Van Bruggen et al (Ann. Med. Interne. (Paris), 1996 147:485-489) teaches that ANAs only specifically bind to nuclear material and Applicant concludes that given this teaching that there is no basis for the present rejection drawn to the cross reactivity of ANAs. The argument has been considered but has not been found persuasive because Examiner is unable to evaluate the information in the reference based only on the submitted abstract.

The arguments have been carefully considered but have not been found persuasive and the newly instituted rejection stands.

8. No claims allowed.

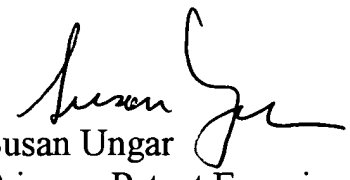
9. All other objections and rejections recited in the previous Action are hereby withdrawn.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
March 16, 2005